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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/596,198	03/09/2007	**Inderjit Singh**	MESC:013US	3351

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Michael R. Krawzsenek
FULBRIGHT & JAWORSKI L.L.P.
600 Congress Avenue, Suite 2400
Austin, TX 78701

EXAMINER	
AUDET, MAURY A	
ART UNIT	**PAPER NUMBER**
1654	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/596,198	SINGH, INDERJIT	
	Examiner	Art Unit	
	MAURY AUDET	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 November 2009*.

2a)☒ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-35,38,39,41-45,55,56,58,59 and 61* is/are pending in the application.

4a) Of the above claim(s) *1-32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *33-35,38,39,41-45,55,56,58,59 and 61* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *6/2/06* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment and response are acknowledged. The amendment necessitated a new, updated search, the art of which is applied below.

Election/Restrictions

As previously noted, Applicant's election without traverse of Group II, claims 33-46 and 48-61 in the reply filed on 11/17/09 is acknowledged (composition and method of use to treat diabetes; it is noted that the method of use was inadvertently grouped with the product claims; but the Examiner will go forward with examination of both in the interests of advancing prosecution).

Claims 1-32 are withdrawn as being drawn to non-elected subject matter.

Independent claim 33 is drawn to a composition comprising two genus classes of molecules:

(a) ANY glutathione donor (with Markush group examples in e.g. dependent claim 36);

PLUS

(b) a Markush group comprising:

i. 3 specific compounds;

ii. a genus 4th compound (ANY inhibitor of HMG-CoA), &

iii. ANY derivative of the compounds of i. or ii. [BUT NOT (a) it is appears]

While independent claim 48 is drawn to a composition comprising the following two genus classes of molecules:

(a) ANY glutathione donor (with Markush group examples in e.g. dependent claim 36);

PLUS

(b) ANY statin – WHICH ARE KNOWN HMG-CoA INHIBITORS (see e.g.

OR

(c) ANY derivative of the (a) or (b) [Versus claim 33, not drawn to any glutathione donor].

It is noted that the Examiner did not require a single compound from (a) and (b) be elected as the invention (e.g. independent and distinct combination). Or even a species election thereof. The Examiner went forward with the search and applied the art below with the understanding that any art on any 1 compound (combination) of all the potential compounds of (a) and (b), would render obvious any other compounds to fall within said genus and/or Markush group; absent evidence to the contrary. As genuses/Markush groups are deemed to all contain the same desired structure and/or properties, to be claimed collectively – since, were this not the case, any combinations falling outside this scope would constitute an independent and distinct invention, to which art on one would not read on the latter. If the latter be the case, Applicant is advised to inform the Office in the next response and proactively elect (and amend the claims to) a single combination as the invention (not species), to which this individual and distinct invention would then be searched. *However, any art found thereon, even if new, would be applied as a Final Rejection.*

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 33-35, 38-39, 41-45, 55-56, 58-59, and 61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Srivastava et al. (US 2004/0047919; GSNO) in view of any/both of Ruderman et al. (US 2003/0212014 A1; AICAR) and Shayman et al. (US 5,302,609; D-PDMP and glycosphingolipid inhibitors, which Miglustat is one of).

The updated search of the art has found that each of the compounds now amended into the base claim is a compound and/or class of compounds known to be used in the treatment of diabetes, the method of use also claimed (see art below). Where compounds are known to be used for the same purpose, even if not expressly combined in the art, it raises a prima facie case of obviousness that it would have been predicable to combine the same for their known use (the applicable case law cited for this general holding is *In re Kerkhoven*). Absent evidence to the

contrary of some unexpected result using any one or more of the latter 3 compounds with the primary compound GSNO.

Srivastava et al. teach use of GSNO to treat diabetes (entire document, especially claims):

> 1. A method of reducing the risk of diabetes complications in a patient comprising administering to the patient an effective amount of a composition comprising a nitric oxide inducer, whereby the amount of nitric oxide in the patient is increased.
>
> Claims Text - CLTX (3):
> 2. The method of claim 1, wherein the nitric oxide inducer is nitric oxide, a nitric oxide precursor, a nitric oxide donor, or an inhibitor of a nitric oxide synthase inhibitor.
>
> Claims Text - CLTX (4):
> 3. The method of claim 2, wherein the composition comprises a nitric oxide precursor.
>
> Claims Text - CLTX (5):
> 4. The method of claim 3, wherein the nitric oxide precursor is L-arginine.
>
> Claims Text - CLTX (6):
> 5. The method of claim 4, wherein the composition comprises a nitric oxide donor.
>
> Claims Text - CLTX (7):
> 6. The method of claim 5, wherein the nitric oxide donor is a nitric oxide synthase substrate, sildenafil citrate, nitroglycerine, S-nitrosoglutathione (**GSNO**), GSSG, or HNE.

Ruderman et al. teach the use of AICAR in the treatment of diabetes (title, entire document):

> [Title] Methods of treating conditions associated with insulin resistance with aicar, (5-amino-4-imidazole carboxamide riboside) and related compounds
>
> [0007] U.S. Pat. No. 5,658,889 discloses that the short-term usage of AICAR in very high doses (500 mg/kg/twice daily) lowers blood glucose levels in control and diabetic rats. This patent also discloses studies in which diabetic rats were treated with such a regimen for 23 days with an apparent

decrease in the severity of the diabetes as judged by lower blood glucose levels and decreased polyuria (i.e., a decrease in the large urine volume).

[0049] Based on these observations, we believe that treatment with AICAR, or a derivative thereof or a related compound, will be useful in particular in patients with insulin resistance or diabetes mellitus, especially non-insulin dependent diabetes mellitus (NIDDM). Treatment with AICAR should diminish damage to the endothelium caused by hyperglycemia and free fatty acids, and for this reason it should be useful in preventing and treating various types of vascular disease associated with metabolic abnormalities, including atherosclerotic vascular disease and, in particular, atherosclerosis associated with diabetes and insulin resistance. By virtue of its effects on glucose and fatty acid metabolism in pericytes, this treatment should also be useful in treating and preventing the microvascular complications of diabetes (such as blindness, retinopathy and possibly nephropathy). Furthermore, AICAR should also prove a useful tool as a chronically administered therapeutic agent in a wide array of situations in which endothelial cell integrity is compromised by stress, e.g., hyperglycemia, high plasma free fatty acid levels and to the extent they are caused by alterations in glucose or fatty acid metabolism possibly ischemia and inflammation.

[0098] From these results, we can also conclude that a single dose of the AMPK activator AICAR leads to an improvement in whole body, muscle and liver insulin sensitivity in high-fat fed rats well beyond the expected time range of activation of AMPK. Also enhanced insulin-mediated glycogen synthesis caused by AICAR occurs in both red and white muscle and does not depend on a period of prior glycogen depletion. AICAR or its derivatives are the prototypes of a new family of compounds for the treatment of hyperglycemia and insulin resistance characteristic of type 2 diabetes and can help in maintaining glucose homeostasis, particularly when other treatments have failed or are no longer successful.

Shayman et al. teach the use of D-PDMP to treat diabetes (entire document):

To determine whether the increase in glucolipid formation in diabetes was functionally important, the following experiment was performed. One group of animals was made diabetic with streptozotocin, and the other group received vehicle alone. After two weeks, the control and diabetic groups were divided according to the weights of the rats. Half of the non-diabetic and half of the diabetic animals received DL-threo-PDMP, which is the racemic mixture of the compound of the Formula I where n is 8. The control non-diabetic and diabetic groups were pair fed and received vehicle alone. After 4 days of treatment the animals were weighed and sacrificed. The characteristics of these animals are

> shown in Table V below. In Table V, the data are expressed as the mean .+-. S.D. All animals received the cytochrome P450 inhibitor piperonyl butoxide (600 mg/kg) intraperitoneally. Treated control and diabetic animals received DL-threo-PDMP.

Shayman et al. also teach the use of any glycosphingolipid inhibitors (col. 2, lines 42-44; entire document). As Applicant acknowledges in the present application para 104, Miglustat is a known glycosphingolipid inhibitor:

> [0104] 1,5-(butylimino)-1,5-dideoxy-D-glucitol (Miglustat) is an inhibitor of glucosylceramide synthase--a glucosyl transferase enzyme that plays a role in the synthesis of many glycosphingolipids. Miglustat is soluble in water. The molecular formula for Miglustat is C.sub.10H.sub.21NO.sub.4 and has a molecular weight of 219.28. The chemical formula for Miglustat is:

[Thus, Shayman et al. intrinsically taught this class of compound and all species therein, absent evidence to the contrary of some unexpected result of Miglustat specifically, in combination with GSNO.]

It would have been obvious to one of ordinary skill in the art at the time of the invention to use any one or more of the compounds AICAR, D-PDMP, or Miglustat in combination with GSNO to treat diabetes in Srivastava et al., because Srivastava et al. teach the advantageous use of GSNO in the treatment of diabetes, and Ruderman et al. and Shayman et al., teach the use of AICAR, D-PDMP, and Miglustat by compound or class, as known for treating diabetes.

Thus, as noted at the outset, the updated search of the art has found that each of the compounds now amended into the base claim is a compound and/or class of compounds known to be used in the treatment of diabetes, the method of use also claimed (see art below). Where compounds are known to be used for the same purpose, even if not

expressly combined in the art, it raises a prima facie case of obviousness that it would have been predicable to combine the same for their known use (the applicable case law cited for this general holding is *In re Kerkhoven*). Absent evidence to the contrary of some unexpected result using any one or more of the latter 3 compounds with the primary compound GSNO.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the reference, especially in the absence of evidence to the contrary.

Conclusion

Applicant's amendment (narrowing to new specific compounds after art rejection) necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MAURY AUDET whose telephone number is (571)272-0960. The examiner can normally be reached on M-Th. 7AM-5:30PM (10 Hrs.).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

MA, 9/27/2010

/Maury Audet/
Primary Examiner, Art Unit 1654